PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
C 2260 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 00597	26/01/2000	27/01/1999
Applicant		
IDEA AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/00597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 25-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/00597

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to novel vaccines for the non-invasine, transcutaneous administration of antigens associated with ultradeformable carriers, for the purpose of prophylactic or therapeutic vaccination. The vaccines comprise (a) a transdermal carrier which is a penetrant, (b) a compound which specifically releases or specifically induces cytokine or anti-cytokine activity or exerts such an activity itself, and (c) an antigen, an allergen, a mixture of antigens and/or mixture of allergens. The invention further relates to methods for the vaccination of mammals for obtaining a protective or therapeutic immune response.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]P 00/00597

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/127 A61K38/19 A61K39/39 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL A, CEVC G: "Non-invasive administration of protein antigens: transdermal immunization with bovine serum albumin in transfersomes" VACCINE RESEARCH, vol. 4, no. 3, 1995, pages 145-164, XP002107365 cited in the application abstract page 147, last paragraph -page 149, paragraph 1 page 153, paragraph 2; figure 5 page 159, paragraph 1 page 162, last paragraph -page 163, paragraph 1 --- -/--	1-7, 10-16, 19-23, 25,26, 28,30, 31,33, 35,36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2000	25/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Marttin, E

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]EP 00/00597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PAUL A ET AL: "Transdermal immunisation with an integral membrane component, gap junction protein, by means of ultradeformable drug carriers, transfersomes" VACCINE, vol. 16, no. 2-3, 2 January 1998 (1998-01-02), page 188-195 XP004098622 cited in the application abstract * page 189, paragraph "Immunogen preparation" * page 194, column 1, line 33 -column 2, line 15	1
A	CEVC G: "Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery" CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, vol. 13, no. 3-4, 1996, pages 257-388, XP002107366 page 316 -page 321	1
A	WO 91 01146 A (PRAXIS BIOLOG INC) 7 February 1991 (1991-02-07) page 3, line 10 -page 4, line 13 page 9, line 17-21 page 10, line 5-11 claims	1-36
A	WO 92 04009 A (UNIV LONDON PHARMACY) 19 March 1992 (1992-03-19) page 1, line 3-7 page 3, line 21-32 page 6-7; example 1 page 14; example 2 claims	1-36
A	GLENN G M ET AL: "Skin immunization made possible by cholera toxin 'letter!" NATURE,GB,MACMILLAN JOURNALS LTD. LONDON, vol. 391, no. 6670, 26 February 1998 (1998-02-26), page 851 XP002110053 ISSN: 0028-0836 cited in the application	1-36

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]P 00/00597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9101146 A	07-02-1991	AU 651949 B	11-08-1994
		AU 6055090 A	22-02-1991
		CA 2063271 A	15-01-1991
		EP 0482068 A	29-04-1992
		JP 4506662 T	19-11-1992
		NO 920160 A	05-03-1992
		US 5334379 A	02-08-1994
WO 9204009 A	19-03-1992	EP 0548210 A	30-06-1993
		JP 6505701 T	30-06-1994

repeated immunogen administration is advocated to maximize the final effect of a therapeutic vaccination. It is proposed to use between 2 and 10, often between 2 and 7, more typically up to 5 and most preferred up to 3 immunizations, when a non-allergenic antigen is used, or such a number of times, in the case of allergens, as is required either to achieve the desired immuno-tolerance, determined as described above or another suitable assessment method, or else to deem the effort as having failed. The time interval between subsequent vaccinations should preferably be between 2 weeks and 5 years, often between 1 month and up to 3 years, more frequently between 2 months and 1.5 years, when a subject is being immunized for the first time. Rodents, such as mice and rabbits are advantageously immunized in 2 weeks interval, primates, e.g., monkeys and often humans, need a booster vaccination in 3-6 months interval.

In a preferred embodiment of the method according to the present invention the flux of penetrants that carry an immunogen through the various pores in a well-defined barrier is determined as a function of a suitable driving force or a pressure acting across the barrier and the data are then conveniently described by a characteristic curve which, in turn, is employed to optimize the formulation or application further.

The invention finally relates to the use of the transdermal carrier, the compound which specifically releases or specifically induces cytokine or anti-cytokine activity or exerts such an activity, the antigen or allergen, and optionally an extract or a compound from a microorganism or a fragment or a derivative thereof, and/or a low molecular weight chemical irritant as defined hereinbefore for the preparation of a vaccine for inducing a protective or tolerogenic immune response.

The figures show:

Figure 1 gives the data on survival of animals immunized epicutaneously with mixed micelles or Transfersomes loaded with TT, to illustrate aggregate size (stability) effect, since the over-destabilized Transfersomes normally disintegrate into the mixed lipid micelles.

In figure 2 the comparison is made between the immune response to conventional lipid vesicles (liposomes) and ultradeformable lipid vesicles (Transfersomes) carrying TT and applied on the skin, the information on corresponding specific antibody concentrations in serum (expressed as absorbance) being given in upper panel.

Figure 3 illustrates the effect of increasing antigen dose on the outcome of epicutaneous immunization by means of Transfersomes, the results being expressed as absorbance change, antibody titre, or animal survival, together with the corresponding specific antibody isotyping data.

Figure 4 highlights the effect of antigen purity on the result of epicutaneous immunization with tetanus toxoid in Transfersomes, including information on time dependence of animal survival.

Figure 5 compares the outcome of repeated invasive (subcutaneous) and non-invasive (epicutaneous) immunization by means of TT in Transfersomes, including animal survival, serum concentration (in terms of absorbance), specific antibody titre, and antibody distribution pattern values.

Figure 6 illustrates the effect of skin pre-treatment (non-specific challenge) on the immune response following Transfersome mediated TT delivery across the skin.

Figure 7 focuses on adjuvant effect of a relatively low-molecular weight immuno-stimulator, monophosphoryl Lipid A (LA), delivered across intact skin together with TT in Transfersomes.

Figure 8 demonstrates the immuno-adjuvancy of a cytokine, interleukin-12 (IL-12) transported across the skin together with TT by means of Transfersomes.

Figure 9 deals with the immuno-modulation by various cytokines of the murine response against TT antigen delivered in Transfersomes non-invasively through the skin.

Figure 10 presents experimental evidence for the immune response stimulation of mice treated on the skin by TT in Transfersomes, when the carriers also include cholera toxin (CT) to support the specific antibody production, and thus animal protection against an otherwise lethal challenge by the tetanus toxin.

Figure 11 illustrates the use of heat labile toxin from E. coli as an immuno-adjuvant.

Figure 12 illustrates the immuno-modulating effect of local skin pre-treatment with histamine in combination with transdermal antigen application with Transfersomes.

Figure 13 demonstrates the effect of subcutaneous priming on anti-tetanus titer and on the survival of epicutaneously vaccinated hosts.

Figure 14 show the effect of bi-valent vaccination with Tetanus Toxoid and Cholera Toxin used as antigens.

The examples illustrate but do not define the limits of the invention.

General experimental set-up and sample preparation

Mice *of Swiss albino* strain (18-20 g) were obtained from The National Institute of Nutrition (Hyderabad, India). They were 8 to 12 weeks old at the time of first immunization and were normally kept in suspension cages in groups of 4 to 6. The animals had free access to standard chow and water. One day prior to an immunization, the application area on murine back was shaved carefully. The antigen was administered with a high precision pipette on the skin surface and left to dry out partially. To prevent immunogen abrasion, the animals were transferred into individual cages in which they were kept for 18 hours following each epicutaneous material administration.

General anesthesia was used to keep the test animals stress free and quiet during manipulations, including immunization. An injection of a mixture of Ketavet and Rompun (0.3 mL per mouse of an isotonic NaCl solution containing 0.0071 % Rompun

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
VOSSIUS & PARTNER
Postfach 86 07 67
D-81634 München
GERMANY

EINGEGANGEN
Vossius & Partner
29. Mai 2000
Frist 25.7.
beard. 25.6.Te

Applicant's or agent's file reference C 2260 PCT	Date of mailing (day/month/year) 25/05/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 00/ 00597	International filing date (day/month/year) 26/01/2000
Applicant IDEA AG	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Nina Vercio

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
C 2260 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 00597	26/01/2000	27/01/1999
Applicant		
IDEA AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/00597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/00597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 25-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/00597

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to novel vaccines for the non-invasine, transcutaneous administration of antigens associated with ultradeformable carriers, for the purpose of prophylactic or therapeutic vaccination. The vaccines comprise (a) a transdermal carrier which is a penetrant, (b) a compound which specifically releases or specifically induces cytokine or anti-cytokine activity or exerts such an activity itself, and (c) an antigen, an allergen, a mixture of antigens and/or mixture of allergens. The invention further relates to methods for the vaccination of mammals for obtaining a protective or therapeutic immune response.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/EP 00/00597

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/127 A61K38/19 A61K39/39 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2000	25/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/EP 00/00597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	CEVC G: "Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery" CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, vol. 13, no. 3-4, 1996, pages 257-388, XP002107366 page 316 -page 321 ---	1
A	WO 91 01146 A (PRAXIS BIOLOG INC) 7 February 1991 (1991-02-07) page 3, line 10 -page 4, line 13 page 9, line 17-21 page 10, line 5-11 claims ---	1-36
A	WO 92 04009 A (UNIV LONDON PHARMACY) 19 March 1992 (1992-03-19) page 1, line 3-7 page 3, line 21-32 page 6-7; example 1 page 14; example 2 claims ---	1-36
A	GLENN G M ET AL: "Skin immunization made possible by cholera toxin 'letter!" NATURE,GB,MACMILLAN JOURNALS LTD. LONDON, vol. 391, no. 6670, 26 February 1998 (1998-02-26), page 851 XP002110053 ISSN: 0028-0836 cited in the application -----	1-36

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/00597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9101146 A	07-02-1991	AU 651949 B	11-08-1994
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		EP 0482068 A	29-04-1992
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		NO 920160 A	05-03-1992
		US 5334379 A	02-08-1994
WO 9204009 A	19-03-1992	EP 0548210 A	30-06-1993
		JP 6505701 T	30-06-1994

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
VOSSIUS & PARTNER
Siebertstrasse 4
81675 München
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
23. Okt. 2000
Frist bearb.: 19.
14.12.

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	19.10.2000
Applicant's or agent's file reference: C 2260 PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00597	26/01/2000	27/01/1999

International Patent Classification (IPC) or both national classification and IPC
A61K9/127

Applicant
IDEA AG

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27/05/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Favre, N

Formalities officer (incl. extension of time limits)
Digiusto, M
Telephone No. +49 89 2399 8162

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-28,32-52	as originally filed			
29,29a,30,30a, 31	as received on	26/05/2000	with letter of	08/05/2000

Claims, No.:

1-36	as originally filed

Drawings, sheets:

1/14-14/14	as received on	26/05/2000	with letter of	08/05/2000

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 25-35 in respect of industrial applicability,

because:

☒ the said international application, or the said claims Nos. 25-35 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 36
Inventive step (IS)	Claims	2-35
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. For the assessment of the present claims 25-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Document D1 (Vaccine Research, 1995, **4**(3):145-164) describes a **transdermal vaccine** (c.f. abstract) using specially optimised ultradeformable agent carriers, named transfersomes™, in combination with different adjuvants. Document D1 shows that the therein described composition elicits a specific immune response in a murine experimental model, when applied transdermally.
As far as it can be understood (see Item VIII), the subject-matter of independent claim 1 does not differ from the disclosure of D1.
Therefore, claim 1 is not novel in the sense of Article 33(2) PCT.

2.1 Dependent claims 2-22 which characterise further embodiments of claim 1, claims 23 and 24 which define kits comprising the vaccine composition of claim 1, and

claims 25-35 which define different uses of the vaccine composition of claim 1 for the generation of a protective immune response do not appear to introduce subject-matter which would render the subject-matter of said claims novel or inventive over the disclosures of D1.
Claims 2-35 thus do not fulfill the requirements of Articles 33(2) and 33(3) PCT.

2.2 Claim 36 refers to the use of any individual compound as defined in any of the preceding claims for the preparation of a vaccine composition which would induce any immune response. Among **many** other examples, claim 36 combined with claim 11 includes any known and unknown vaccine.
Claim 36 is therefore not novel in the sense of Article 33(2) PCT.

3. Given that transdermal vaccines which elicit an immune response are known in the prior art and that it is currently not possible to define how the vaccine composition of the present application differ from the prior art, no technical problem to be solved by the present application can be identified (see also page 7, lines 13-16 of the description).
Should the claims be amended such as to establish novelty, the applicant is invited to indicate which technical problem is addressed by said amended claims.

Re Item VIII

Certain observations on the international application

1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved.

1.1 Moreover, claim 1 is not supported by the description as required by Article 6 PCT, as its scope is much broader than justified by the description and drawings, in which only one embodiment which allows the performance of the claimed invention is disclosed, i.e. the use of transfersomes™. Furthermore, some of the

conventional lipid vesicles described in the comparative examples also fall within the broad wording of the claim. It is generally accepted that the disclosure of one way of performing an invention is only sufficient if it allows the invention to be performed in the **whole range claimed** rather than only some members of the claimed class to be obtained.

1.2 In addition, as sufficiency of disclosure thus presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims, the present application does not meet the requirements of Article 5 PCT.

1.3 The applicant should note that it is well accepted that the protection conferred by a patent should correspond to the technical contribution to the art made by the disclosure of the invention described therein. Hence, this excludes the patent monopoly being extended to subject-matter which, after reading the patent specification, would still not be at the disposal of the skilled person. The available information has to enable the skilled person to achieve the envisaged result within the whole ambit of the claim containing the respective functional definition without undue difficulty, and the description with or without the relevant common general knowledge has to provide a fully self-sufficient technical concept as to how this result was to be achieved.

2. The extensive use in the claims of the expressions "one or more", "preferably", "and/or", "in particular", "such as", "like", "etc.", "often" and of similar formulations renders the determination of the exact nature of the protection sought nearly impossible. Therefore, claims 1-36 lack clarity in the sense of Article 6 PCT.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Siebertstrasse 4
81675 München
ALLEMAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	04.04.2001
Applicant's or agent's file reference C 2260 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00597	26/01/2000	27/01/1999

Applicant
IDEA AG

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 September 2000 (28.09.00)	
International application No. PCT/EP00/00597	**Applicant's or agent's file reference** C 2260 PCT
International filing date (day/month/year) 26 January 2000 (26.01.00)	**Priority date** (day/month/year) 27 January 1999 (27.01.99)
Applicant CEVC, Gregor et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 August 2000 (24.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2260 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00597	26/01/2000	27/01/1999
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant IDEA AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 19 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/08/2000	04.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Favre, N Telephone No. +49 89 2399 7363

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/00597

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, pages:

1-28,32-52	as originally filed			
29,29a,30,30a, 31	as received on	02/11/2000	with letter of	08/05/2000

Claims, No.:

1-36	as originally filed			

Drawings, sheets:

1/14-14/14	as received on	02/11/2000	with letter of	08/05/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 25-35, with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 25-35 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-35
	No:	Claims	36
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-24 and 36
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. For the assessment of the present claims 25-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Document D1 (Vaccine Research, 1995, **4**(3):145-164) describes a **transdermal vaccine** (cf. abstract) using specially optimised ultradeformable agent carriers, named transfersomes™, in combination with different adjuvants. Document D1 shows that the therein described composition elicits a specific immune response in a murine experimental model, when applied transdermally.
   As far as it can be understood (see Item VIII) and according to the applicant's arguments, the subject-matter of independent claim 1 differs from the disclosure

of D1 in that a compound which specifically releases or induces cytokine or anti-cytokine activity, or exerts such an activity itself (see claim 1(b)) is present in the claimed composition (see claim 8 for examples of such compounds).
According to the applicant this feature allows the successful induction of a medically useful transdermal immune response (see also page 7, lines 13-16 of the description).
However, the sole example using the compounds as required by claim 1 (b) which has provided in the application as filed is the set of experiments illustrated in Figure 9. As can be read in the legend of said Figure 9, **no protection was observed in these experiments**.
Therefore, the composition defined in independent claim 1 fails to solve the above stated technical problem and hence cannot be considered as being inventive in the sense of Article 33(3) PCT.

2.1 Dependent claims 2-22 which characterise further embodiments of claim 1, claims 23 and 24 which define kits comprising the vaccine composition of claim 1, and claims 25-35 which define different uses of the vaccine composition of claim 1 for the generation of a protective immune response do not appear to introduce subject-matter which would render the subject-matter of said claims inventive in view of the disclosures of D1.
Claims 2-35 thus do not fulfill the requirements of Article 33(3) PCT.

2.2 Claim 36 refers to the use of any **individual** compound as defined in any of the preceding claims for the preparation of a vaccine composition which would induce any immune response. Among **many** other examples, claim 36 combined with claim 11 includes any known and unknown vaccine.
Claim 36 is therefore not novel in the sense of Article 33(2) PCT.

Re Item VIII

Certain observations on the international application

1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved.

1.1 Moreover, claim 1 is not supported by the description as required by Article 6 PCT, as its scope is much broader than justified by the description and drawings, in which only one embodiment which allows the performance of the claimed invention is disclosed, i.e. the use of transfersomes™. Furthermore, some of the conventional lipid vesicles described in the comparative examples also fall within the broad wording of the claim. It is generally accepted that the disclosure of one way of performing an invention is only sufficient if it allows the invention to be performed in the **whole range claimed** rather than only some members of the claimed class to be obtained (see also Item V).

1.2 In addition, as sufficiency of disclosure thus presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims, the present application does not meet the requirements of Article 5 PCT (see also Item V).

2. The extensive use in the claims of the expressions "one or more", "preferably", "and/or", "in particular", "such as", "like", "etc.", "often" and of similar formulations renders the determination of the exact nature of the protection sought nearly impossible. Therefore, claims 1-36 lack clarity in the sense of Article 6 PCT.

repeated immunogen administration is advocated to maximize the final effect of a therapeutic vaccination. It is proposed to use between 2 and 10, often between 2 and 7, more typically up to 5 and most preferred up to 3 immunizations, when a non-allergenic antigen is used, or such a number of times, in the case of allergens, as is required either to achieve the desired immuno-tolerance, determined as described above or another suitable assessment method, or else to deem the effort as having failed. The time interval between subsequent vaccinations should preferably be between 2 weeks and 5 years, often between 1 month and up to 3 years, more frequently between 2 months and 1.5 years, when a subject is being immunized for the first time. Rodents, such as mice and rabbits are advantageously immunized in 2 weeks interval, primates, e.g., monkeys and often humans, need a booster vaccination in 3-6 months interval.

In a preferred embodiment of the method according to the present invention the flux of penetrants that carry an immunogen through the various pores in a well-defined barrier is determined as a function of a suitable driving force or a pressure acting across the barrier and the data are then conveniently described by a characteristic curve which, in turn, is employed to optimize the formulation or application further.

The invention finally relates to the use of the transdermal carrier, the compound which specifically releases or specifically induces cytokine or anti-cytokine activity or exerts such an activity, the antigen or allergen, and optionally an extract or a compound from a microorganism or a fragment or a derivative thereof, and/or a low molecular weight chemical irritant as defined hereinbefore for the preparation of a vaccine for inducing a protective or tolerogenic immune response.

~~The figures show:~~

Figure 1 gives the data on survival of ~~animals~~ immunized epicutaneously with mixed micelles or Transfersomes loaded with TT, to illustrate aggregate size (stability) effect; ~~since the over-destabilized Transfersomes normally disintegrate into the mixed lipid micelles.~~

The figures show:

Figure 1: Mixed micelles versus Transfersomes. The figure gives the data on survival of animals immunised epicutaneously with mixed micelles or Transfersomes loaded with purified TT, to illustrate aggregate size (stability) effect, since the over-destabilised Transfersomes normally disintegrate into the mixed lipid micelles.

Figure 2: Liposomes versus Transfersomes. A comparison is made between the immune response to conventional lipid vesicles (liposomes) and ultradeformable lipid vesicles (Transfersomes) carrying purified TT and applied on the skin. The information on corresponding specific antibody concentrations in serum (expressed as absorbance) is given in the upper panel.

Figure 3: Antigen dose effect. The figure illustrates the effect of increasing antigen dose on the outcome of epicutaneous immunisation by means of Transfersomes from SPC:NaChol (3.75:1) loaded with antigen and monophosphoryl lipid A (LA).The results are expressed as absorbance change, antibody titre, or animal survival, together with the corresponding specific antibody isotyping data. Antigen doses were 10, 20, 40 and 80 μg. 6 animals per each group except for No Ag (4 animals) were used.

Figure 4: Antigen purity effect. The figure highlights the effect of antigen purity on the result of epicutaneous immunisation with 80 μg tetanus toxoid and monophosphoryl lipid A (LA) in Transfersomes from SPC:NaCh (3.75:1), including information on time dependence of animal survival. All data were obtained after the 2nd boost + 7 days.

Figure 5: Epicutaneous versus subcutaneous immunization. The figure compares the outcome of repeated invasive (subcutaneous) and non-invasive (epicutaneous) immunisation by means of TT in Transfersomes, including animal

survival, serum concentration (in terms of absorbance), specific antibody titre, and antibody distribution pattern values.

Figure 6: Pre-injection effect. The figure illustrates the effect of skin pre-treatment (non-specific challenge) on the immune response following Transfersome (SPC:Tw-80 1:1) mediated TT (40 μg) delivery across the skin. Mice in the preinjection groups were injected 24 hours before the application of 40 μg antigen. 0.1 ml each of saline (pre-S), 10% SPC:NaCh 4.5:1 empty Transfersomes (Pre-empty Tfs), and incomplete Freund's adjuvant were used for pre-injection. All mice in this experiment were challenged with 50 times LD50 dose of toxin 7 days after the second boost. It means (ec) epicutaneous, (sc) subcutaneous, and (Tfs) Transfersomes.

Figure 7: Adjuvant effect: for example monophosphoryl lipid A. The figure focuses on adjuvant effect of a relatively low-molecular weight immuno-stimulator, monophosphoryl Lipid A (LA), delivered across intact skin together with TT in Transfersomes.

Figure 8: Adjuvant effect: for example cytokine IL-12. The figure demonstrates the immuno-adjuvancy of a cytokine, interleukin-12 (IL-12) transported across the skin (ec) together with TT by means of Transfersomes from SPC:NaCh.

Figure 9: Immunomodulant effect, for example cytokines. The figure deals with the immuno-modulation by various cytokines of the murine response against impure tetanus toxoid (TT) antigen delivered in Transfersomes non-invasively through the skin. Serum was collected for the assay on the 7th day after 2nd boost. No protection was observed in any of the groups.

Figure 10: Immunoadjuvant effect: for example cholera toxin (CT). The figure presents experimental evidence for the immune response stimulation of mice treated on the skin by pure tetanus toxoid (TT) in Transfersomes (SPC:NaCh 3.75:1), when the carriers also include 10 μg cholera toxin (CT) to support the

specific antibody production, and thus animal protection against an otherwise lethal challenge by the tetanus toxin. 4-6 animals per group were used. The asterisc indicates 1 paralyzed mouse out of 4.

Figure 11 Adjuvant effect: for example heat labile toxin (HLT) from E.coli. The figure illustrates the use of heat labile toxin from E. coli as an immuno-adjuvant.

Figure 12: Histamine effect: on anti-tetanus titer and survival after immunization with Transfersomes on the skin. The figure illustrates the immuno-modulating effect of local skin pre-treatment with histamine in combination with transdermal antigen application with Transfersomes.

Figure 13: Subcutaneous priming: effect on anti-tetanus titer and survival after epicutaneous boosts. The figure demonstrates the effect of subcutaneous priming on anti-tetanus titer and on the survival of epicutaneously vaccinated hosts.

Figure 14: Bi-valent vaccines: Anti-Tetanus and anti-Cholera response to the administration of both antigens together in Transfersomes on the skin. The figure shows the effect of bi-valent vaccination with Tetanus Toxoid nad Cholera Toxin used as antigens.

~~Figure 10 presents experimental evidence for the immune response stimulation of~~ mice treated on the skin by TT in Transfersomes, when the carriers also include cholera toxin (CT) to support the specific antibody production, and thus animal protection against an otherwise lethal challenge by the tetanus toxin.

Figure 11 illustrates the use of heat labile toxin from E. coli as an immuno-adjuvant.

Figure 12 illustrates the immuno-modulating effect of local skin pre-treatment with histamine in combination with transdermal antigen application with Transfersomes.

Figure 13 demonstrates the effect of subcutaneous priming on anti-tetanus titer and on the survival of epicutaneously vaccinated hosts.

Figure 14 show the effect of bi-valent vaccination with Tetanus Toxoid and Cholera ~~Toxin used as antigens.~~

The examples illustrate but do not define the limits of the invention.

General experimental set-up and sample preparation

***Mice** of Swiss albino* strain (18-20 g) were obtained from The National Institute of Nutrition (Hyderabad, India). They were 8 to 12 weeks old at the time of first immunization and were normally kept in suspension cages in groups of 4 to 6. The animals had free access to standard chow and water. One day prior to an immunization, the application area on murine back was shaved carefully. The antigen was administered with a high precision pipette on the skin surface and left to dry out partially. To prevent immunogen abrasion, the animals were transferred into individual cages in which they were kept for 18 hours following each epicutaneous material administration.

General anesthesia was used to keep the test animals stress free and quiet during manipulations, including immunization. An injection of a mixture of Ketavet and Rompun (0.3 mL per mouse of an isotonic NaCl solution containing 0.0071 % Rompun

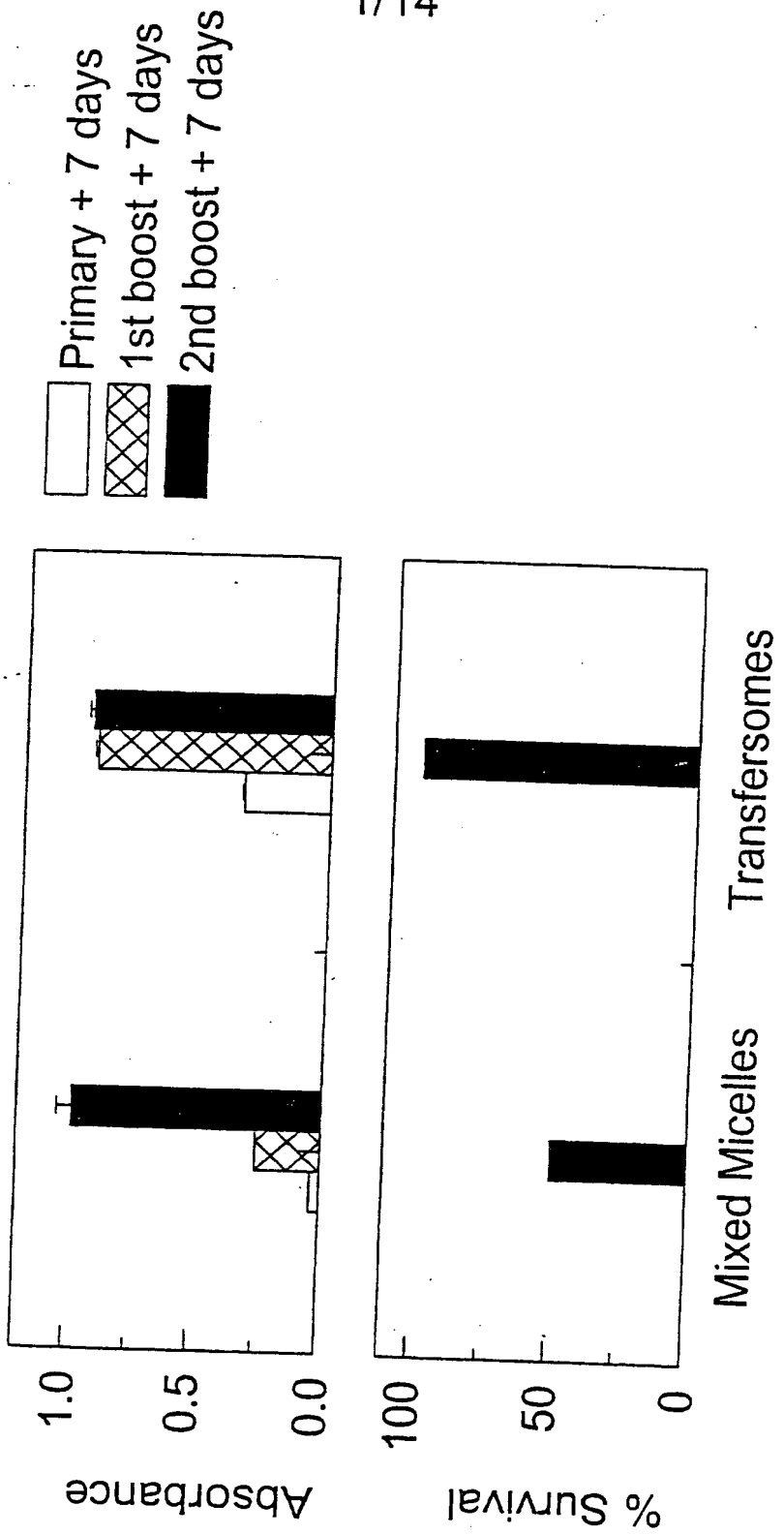

Primary + 7 days
1st boost + 7 days
2nd boost + 7 days
Absorbance
1.0
0.5
0.0
% Survival
100
50
0
Mixed Micelles
Transfersomes

Fig. 1

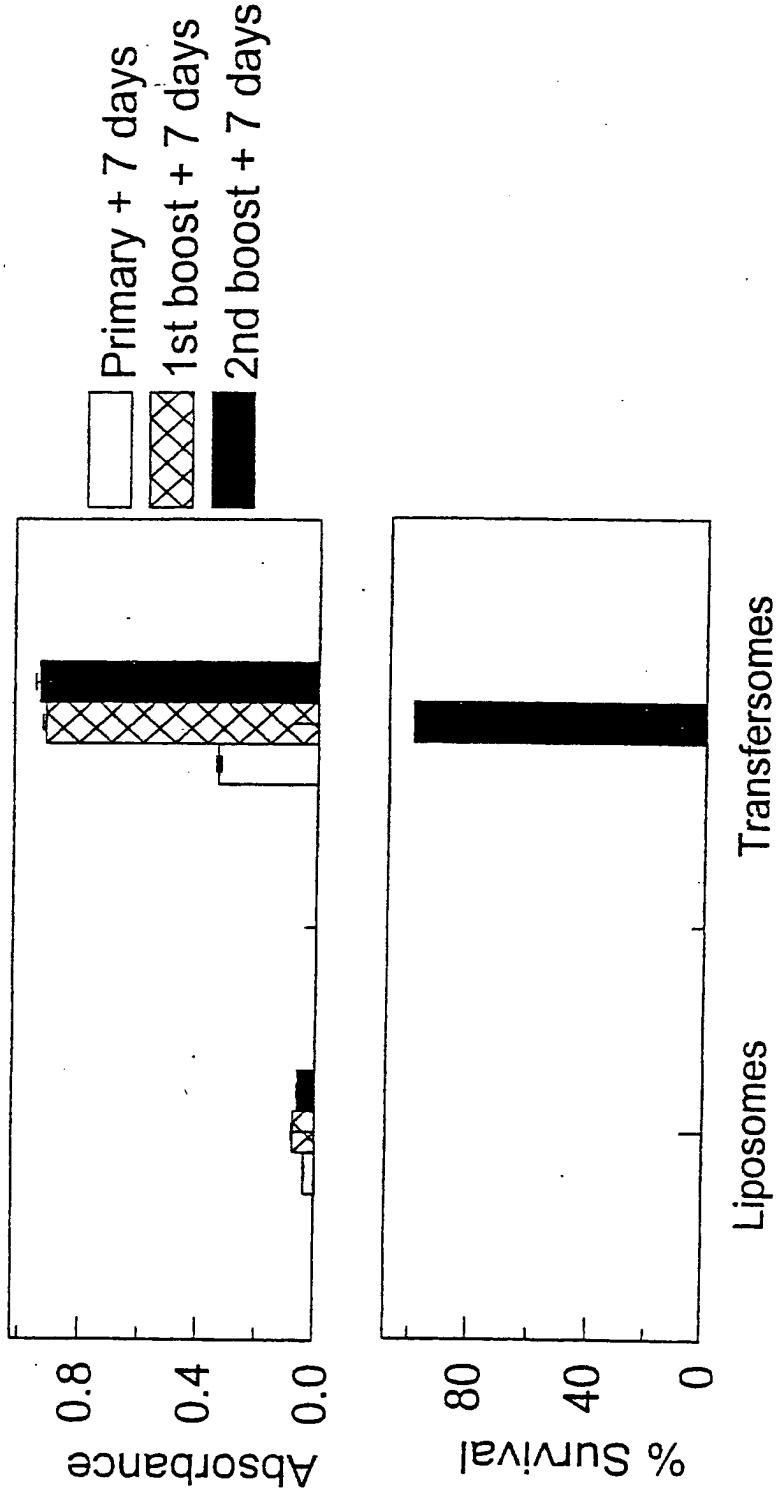

Primary + 7 days
1st boost + 7 days
2nd boost + 7 days
Absorbance
0.0
0.4
0.8
% Survival
0
40
80
Liposomes
Transfersomes

Fig. 2

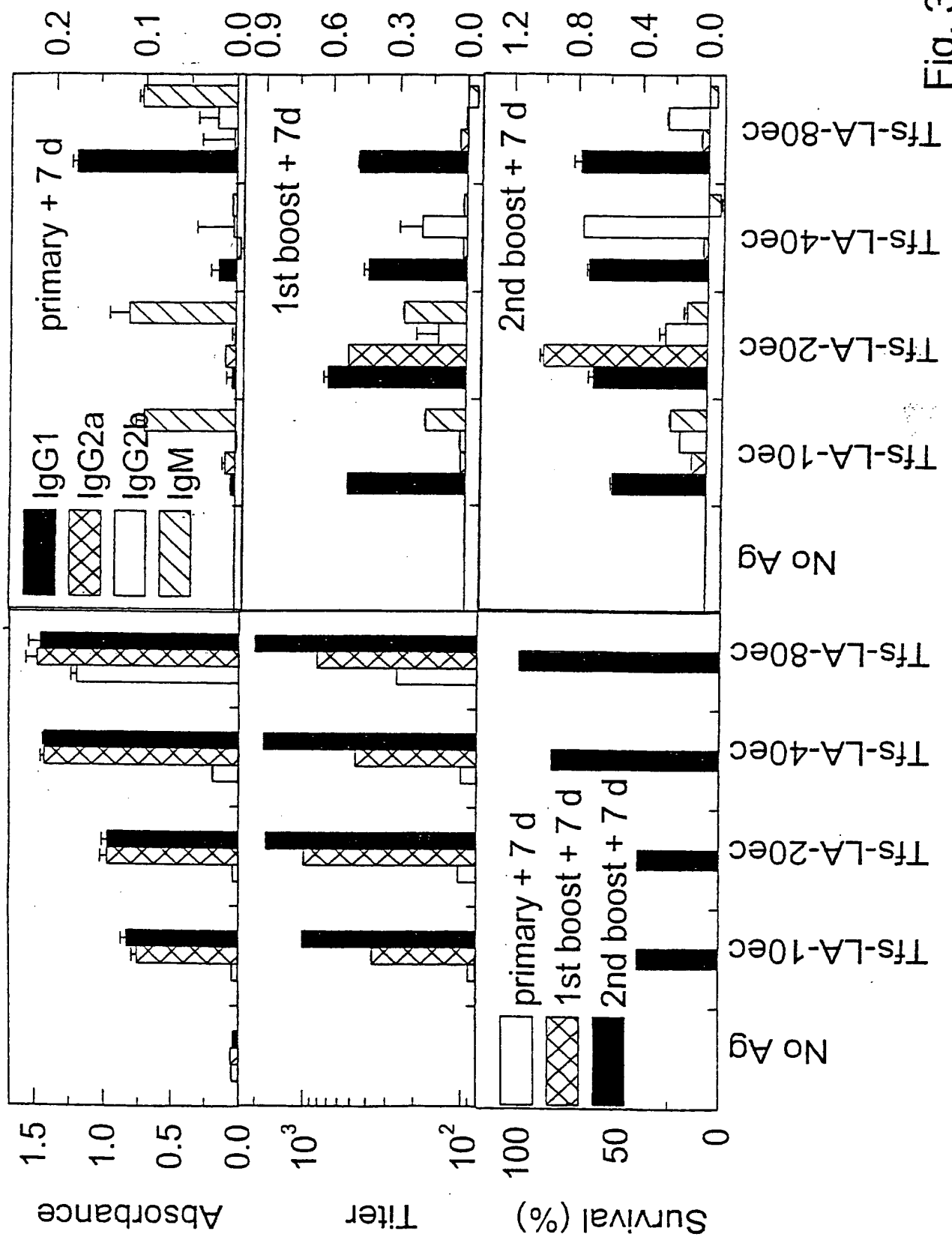

Absorbance
primary + 7 d
1st boost + 7d
2nd boost + 7 d
IgG1
IgG2a
IgG2b
IgM
No Ag
Tfs-LA-10ec
Tfs-LA-20ec
Tfs-LA-40ec
Tfs-LA-80ec
Survival (%)
Titer
Absorbance
primary + 7 d
1st boost + 7 d
2nd boost + 7 d

Fig. 3

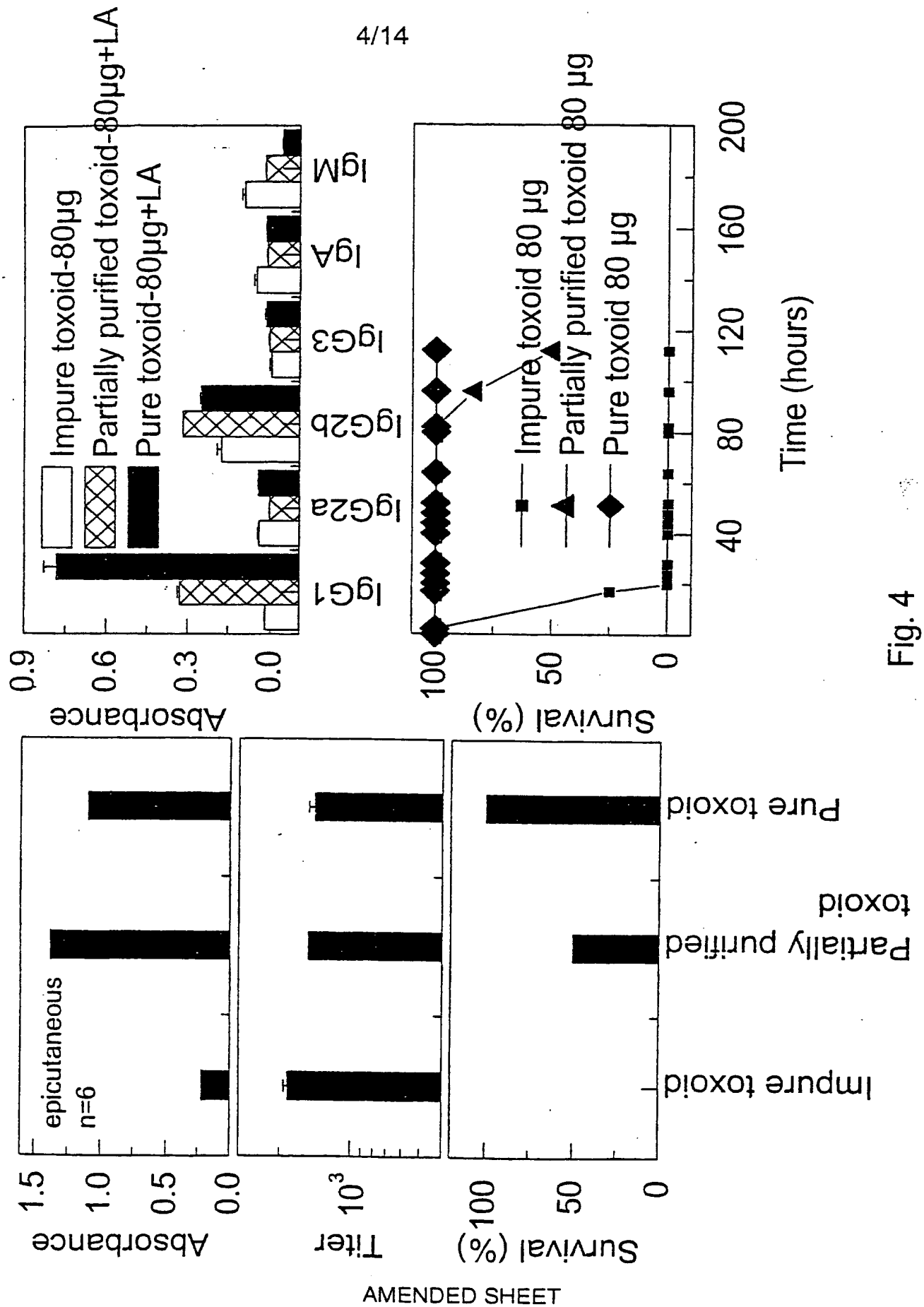

Absorbance
epicutaneous
n=6
Titer
10^3
Survival (%)
Impure toxoid
Partially purified toxoid
Pure toxoid
Impure toxoid-80µg
Partially purified toxoid-80µg+LA
Pure toxoid-80µg+LA
IgG1
IgG2a
IgG2b
IgG3
IgA
IgM
Impure toxoid 80 µg
Partially purified toxoid 80 µg
Pure toxoid 80 µg
Time (hours)

Fig. 4

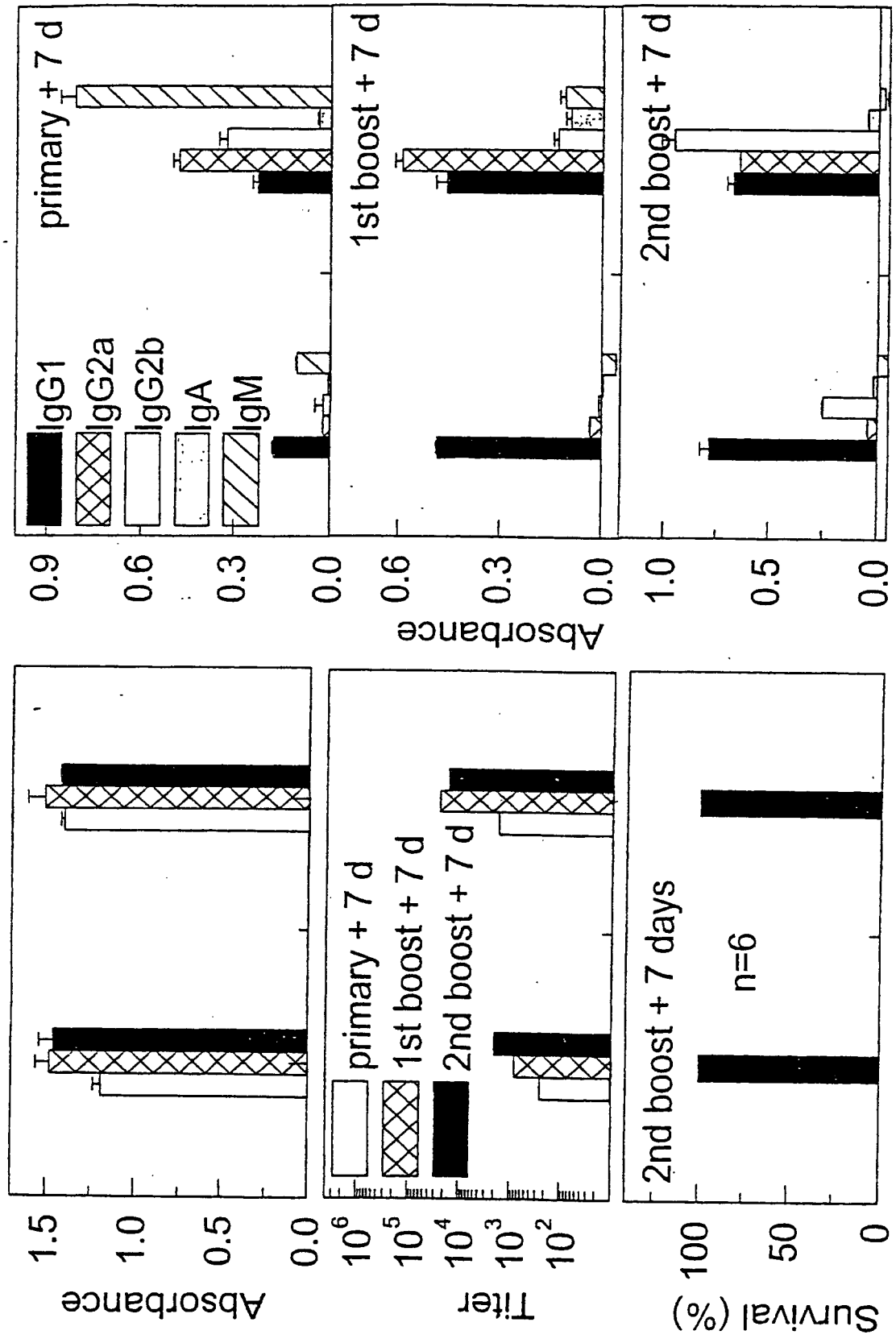

primary + 7 d
1st boost + 7 d
2nd boost + 7 d
IgG1
IgG2a
IgG2b
IgA
IgM
Absorbance
0.9
0.6
0.3
0.0
1.0
0.5
epicutaneous subcutaneous
pure tetanus toxoid
Titer
10^6
10^5
10^4
10^3
10^2
2nd boost + 7 days
n=6
Survival (%)
100
50
0
epicutaneous subcutaneous
pure tetanus toxoid

Fig. 5

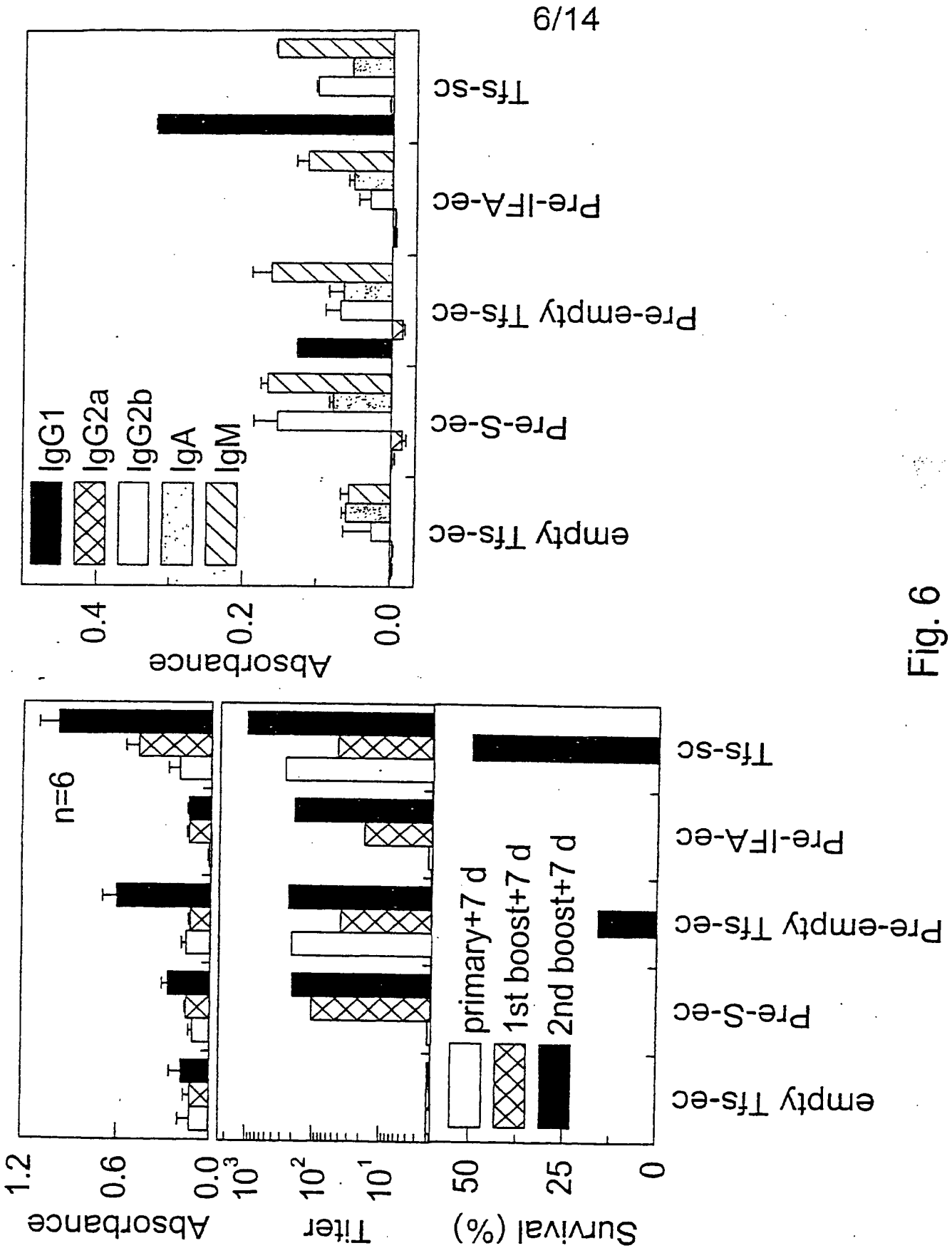

Survival (%)
Titer
Absorbance
primary+7 d
1st boost+7 d
2nd boost+7 d
n=6
IgG1
IgG2a
IgG2b
IgA
IgM
empty Tfs-ec
Pre-S-ec
Pre-empty Tfs-ec
Pre-IFA-ec
Tfs-sc

Fig. 6

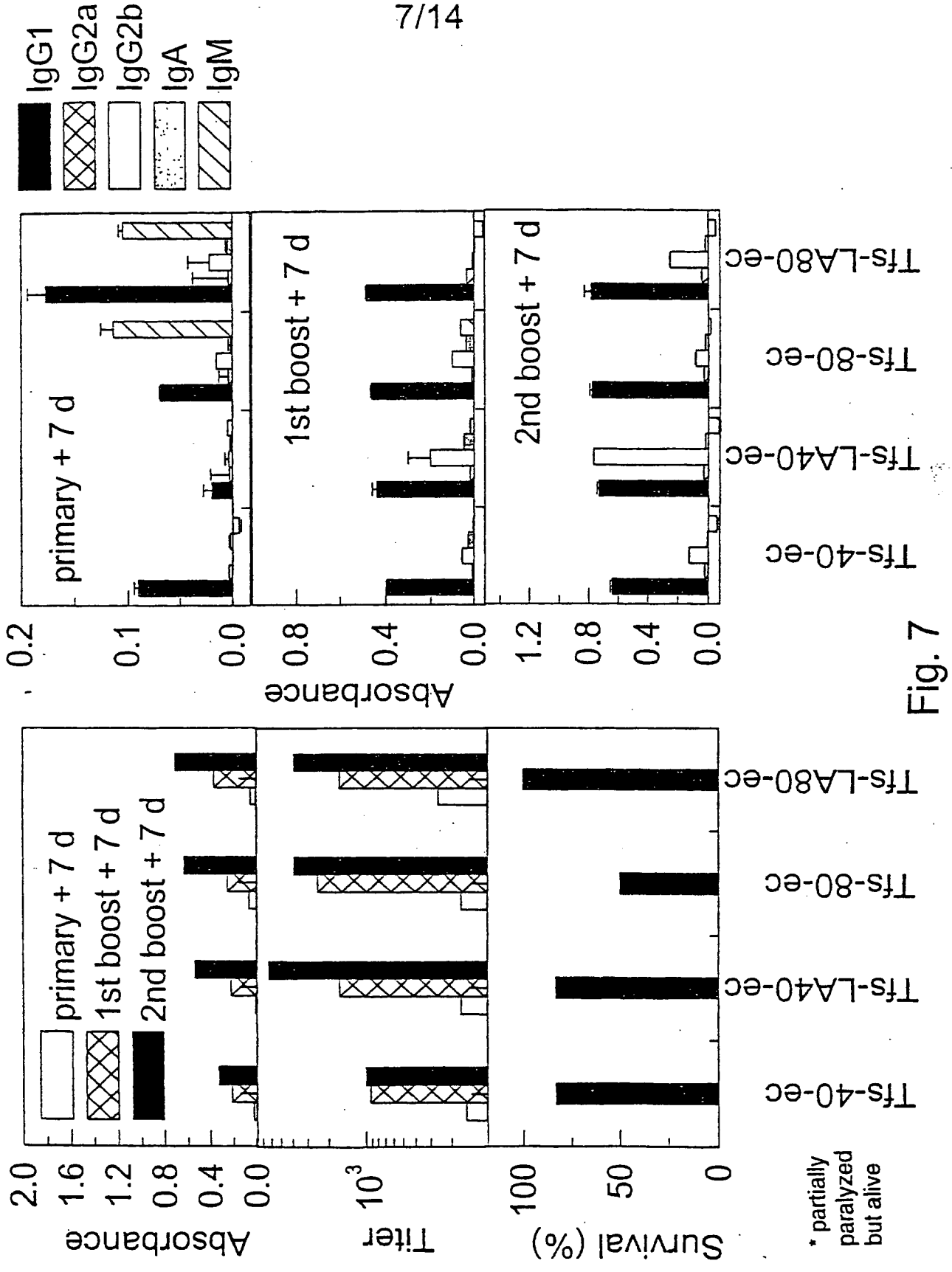

IgG1
IgG2a
IgG2b
IgA
IgM
primary + 7 d
1st boost + 7 d
2nd boost + 7 d
Absorbance
0.2
0.1
0.0
0.8
0.4
0.0
1.2
0.8
0.4
0.0
Tfs-LA80-ec
Tfs-80-ec
Tfs-LA40-ec
Tfs-40-ec
primary + 7 d
1st boost + 7 d
2nd boost + 7 d
Absorbance
2.0
1.6
1.2
0.8
0.4
0.0
Titer
10^3
Survival (%)
100
50
0
* partially paralyzed but alive
Tfs-LA80-ec
Tfs-80-ec
Tfs-LA40-ec
Tfs-40-ec

Fig. 7

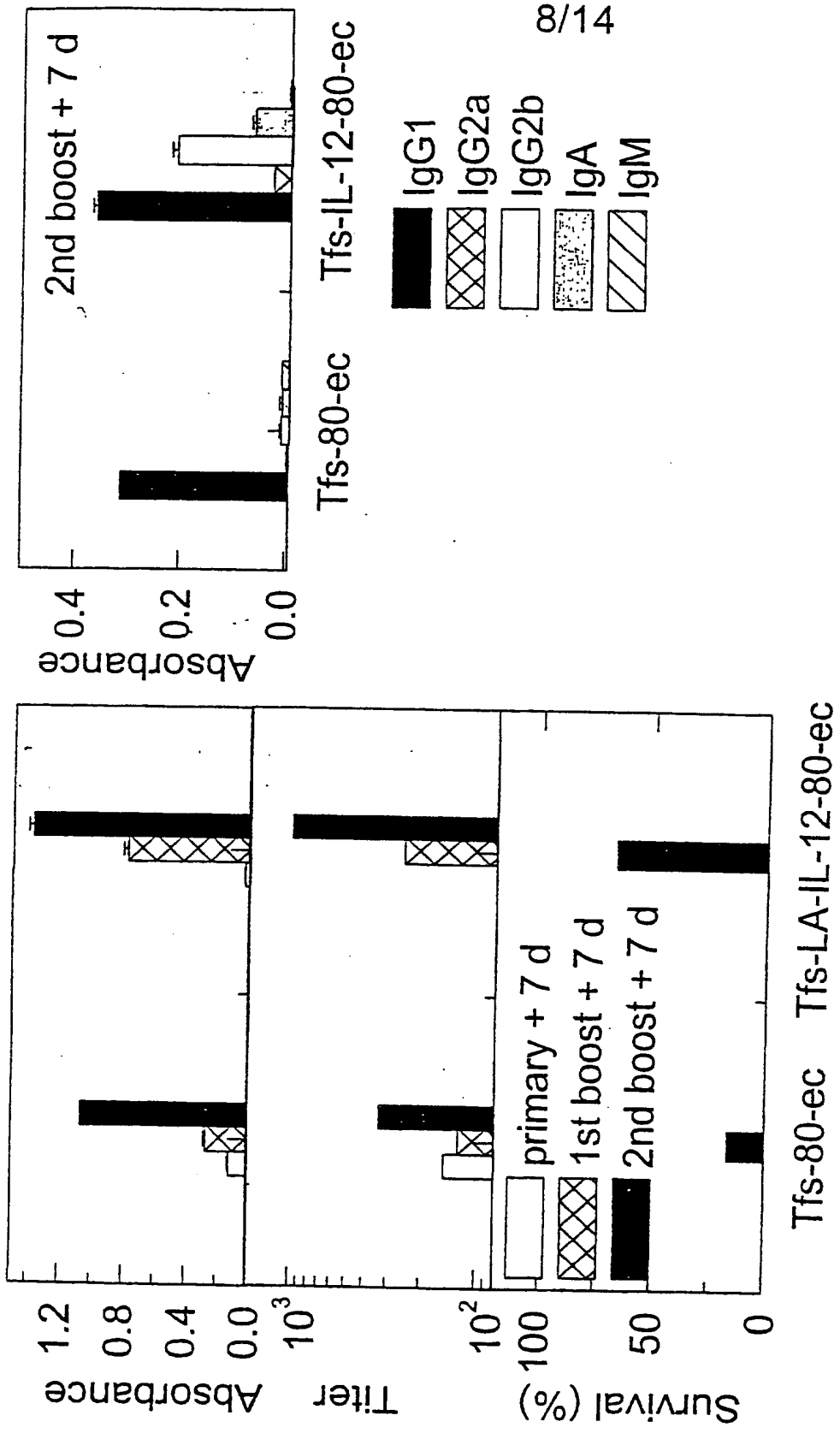

Survival (%)
Titer
Absorbance
primary + 7 d
1st boost + 7 d
2nd boost + 7 d
Tfs-80-ec
Tfs-LA-IL-12-80-ec
2nd boost + 7 d
Absorbance
Tfs-80-ec
Tfs-IL-12-80-ec
IgG1
IgG2a
IgG2b
IgA
IgM

Fig. 8

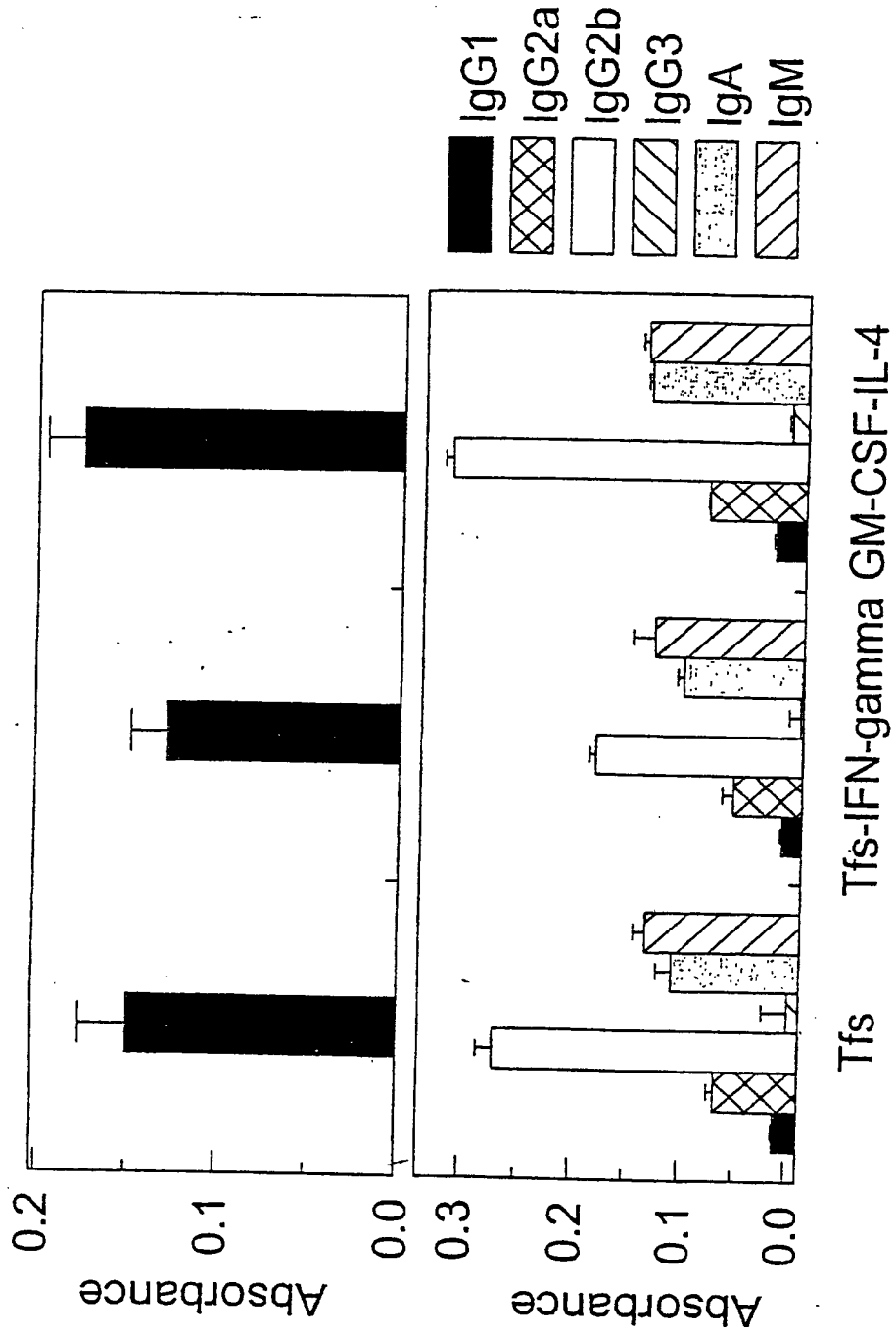

IgG1
IgG2a
IgG2b
IgG3
IgA
IgM
Absorbance
0.2
0.1
0.0
Absorbance
0.3
0.2
0.1
0.0
Tfs
Tfs-IFN-gamma GM-CSF-IL-4

Fig. 9

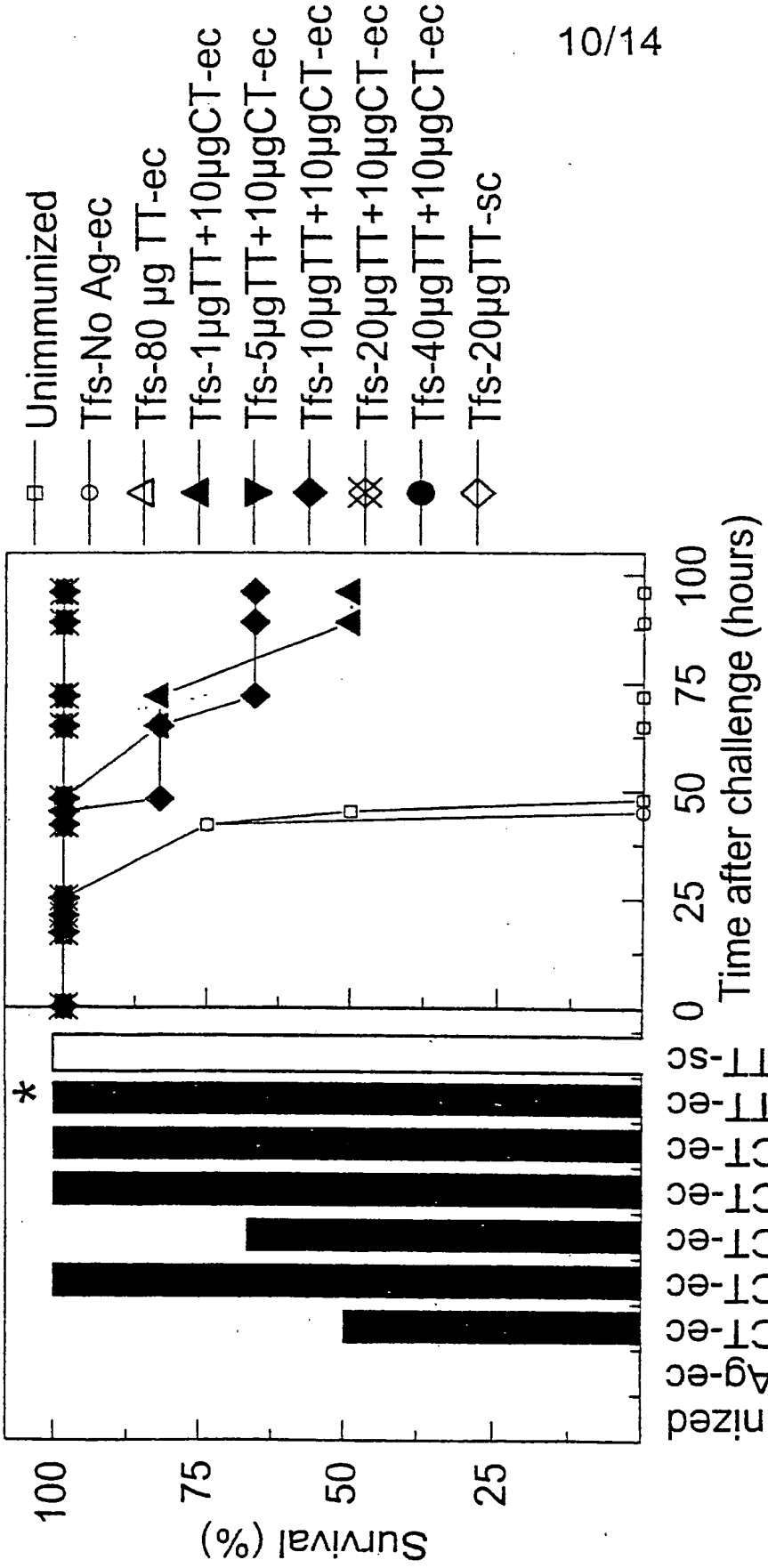

Survival (%)
100
75
50
25
0
25
50
75
100
Time after challenge (hours)
Unimmunized
Tfs-No Ag-ec
Tfs-1µgTT+CT-ec
Tfs-5µgTT+CT-ec
Tfs-10µgTT+CT-ec
Tfs-20µgTT+CT-ec
Tfs-40µgTT+CT-ec
Tfs-80µgTT-ec
Tfs-20µgTT-sc
*
Unimmunized
Tfs-No Ag-ec
Tfs-80 µg TT-ec
Tfs-1µgTT+10µgCT-ec
Tfs-5µgTT+10µgCT-ec
Tfs-10µgTT+10µgCT-ec
Tfs-20µgTT+10µgCT-ec
Tfs-40µgTT+10µgCT-ec
Tfs-20µgTT-sc

Fig. 10

11/14

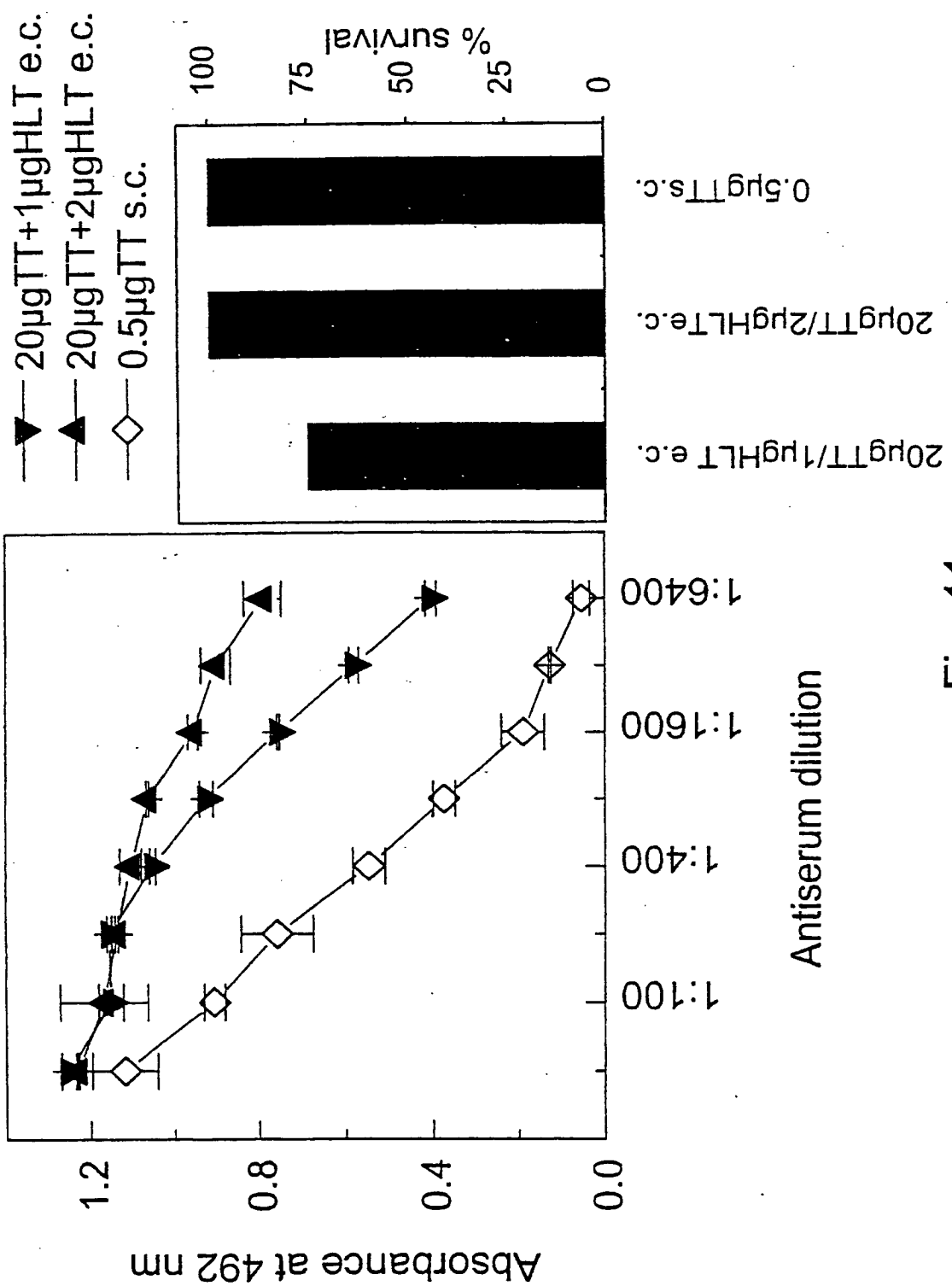
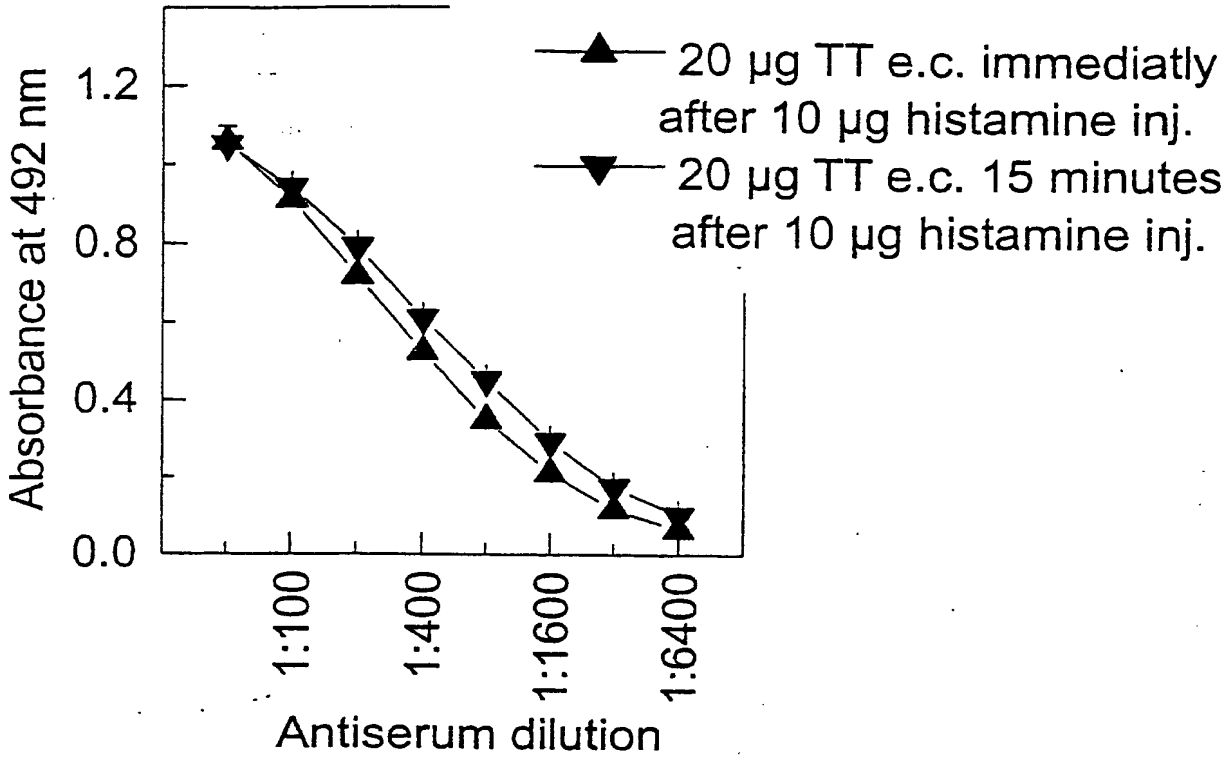

20µgTT+1µgHLT e.c.
20µgTT+2µgHLT e.c.
0.5µgTT s.c.
% survival
100
75
50
25
0
0.5µgTT s.c.
20µgTT/2µgHLT e.c.
20µgTT/1µgHLT e.c.
Absorbance at 492 nm
1.2
0.8
0.4
0.0
1:100
1:400
1:1600
1:6400
Antiserum dilution

Fig. 11


Absorbance at 492 nm
1.2
0.8
0.4
0.0
1:100
1:400
1:1600
1:6400
Antiserum dilution
20 µg TT e.c. immediatly after 10 µg histamine inj.
20 µg TT e.c. 15 minutes after 10 µg histamine inj.

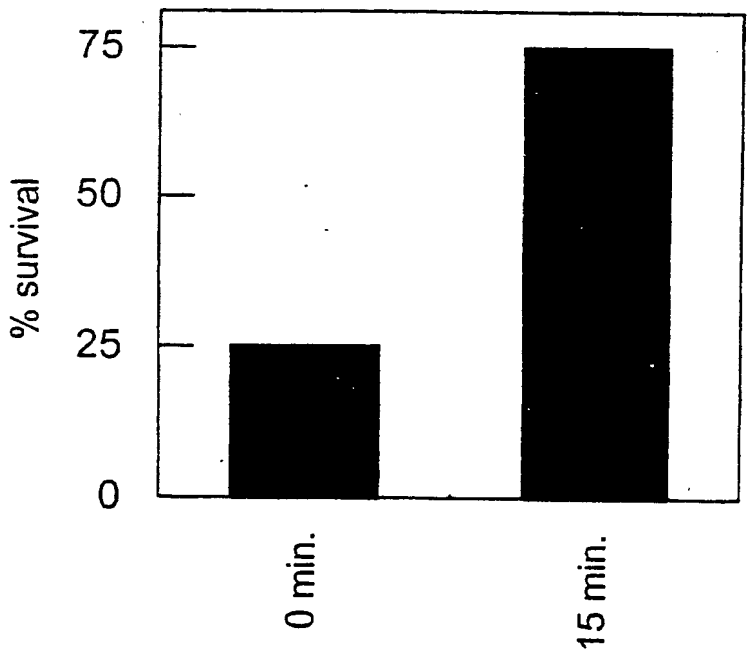

% survival
75
50
25
0
0 min.
15 min.

Fig. 12

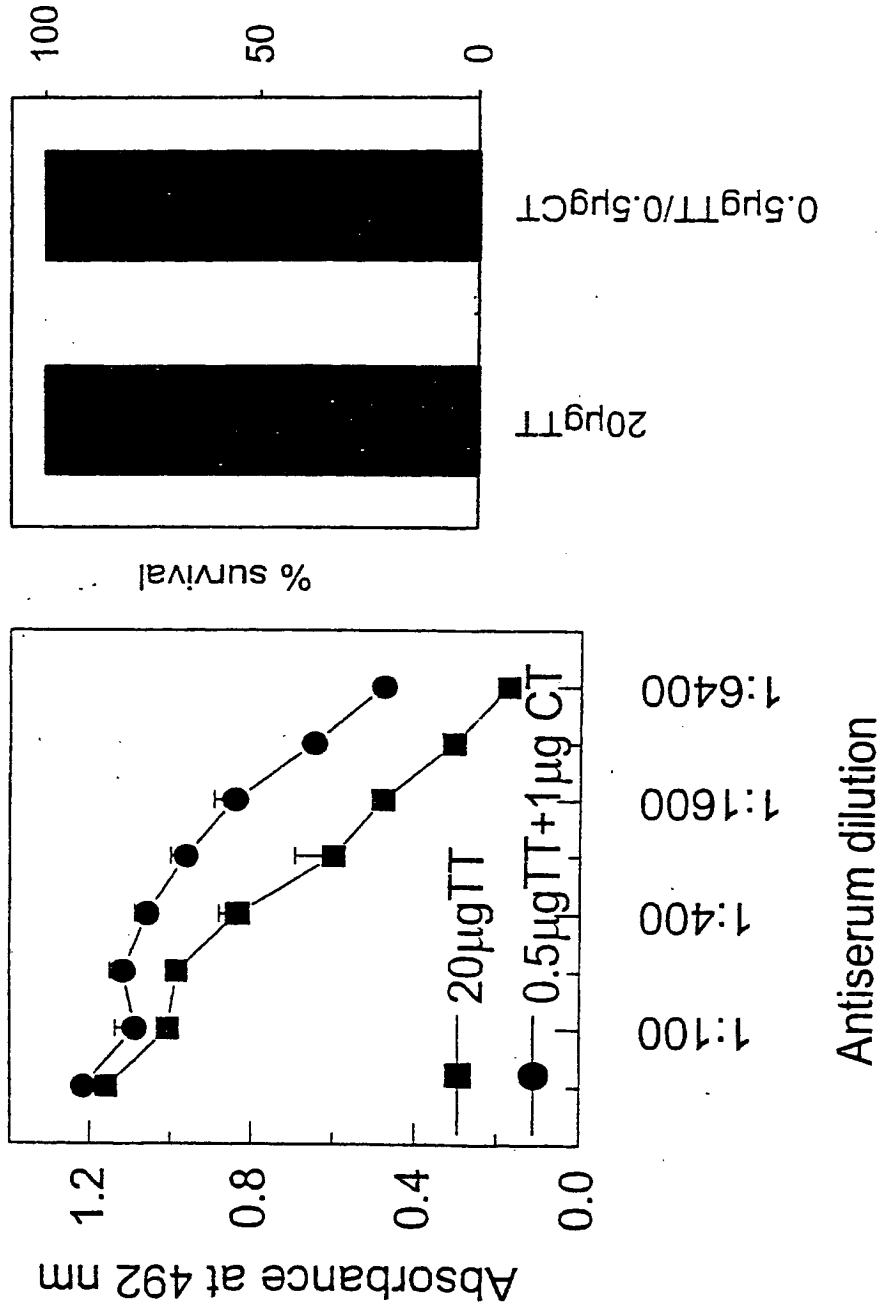

100
50
0
0.5µgTT/0.5µgCT
20µgTT
% survival
Absorbance at 492 nm
1.2
0.8
0.4
0.0
20µgTT
0.5µgTT+1µg CT
1:100
1:400
1:1600
1:6400
Antiserum dilution

Fig. 13

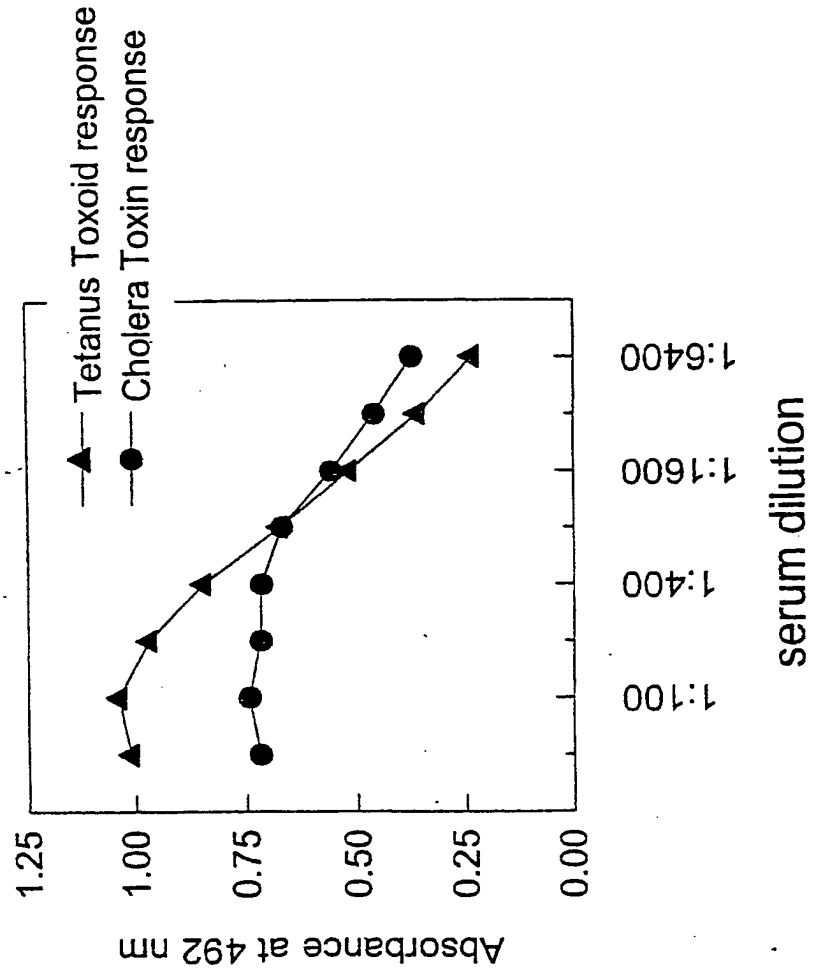

Tetanus Toxoid response
Cholera Toxin response
Absorbance at 492 nm
1.25
1.00
0.75
0.50
0.25
0.00
serum dilution
1:100
1:400
1:1600
1:6400

Fig. 14

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2260 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00597	26/01/2000	27/01/1999
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant IDEA AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 19 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/08/2000	04.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Favre, N Telephone No. +49 89 2399 7363

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/00597

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-28,32-52	as originally filed			
29,29a,30,30a, 31	as received on	02/11/2000	with letter of	08/05/2000

Claims, No.:

1-36	as originally filed			

Drawings, sheets:

1/14-14/14	as received on	02/11/2000	with letter of	08/05/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 25-35, with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 25-35 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-35
	No:	Claims	36
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-24 and 36
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. For the assessment of the present claims 25-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Document D1 (Vaccine Research, 1995, **4**(3):145-164) describes a **transdermal vaccine** (cf. abstract) using specially optimised ultradeformable agent carriers, named transfersomes™, in combination with different adjuvants. Document D1 shows that the therein described composition elicits a specific immune response in a murine experimental model, when applied transdermally.
   As far as it can be understood (see Item VIII) and according to the applicant's arguments, the subject-matter of independent claim 1 differs from the disclosure

of D1 in that a compound which specifically releases or induces cytokine or anti-cytokine activity, or exerts such an activity itself (see claim 1(b)) is present in the claimed composition (see claim 8 for examples of such compounds).
According to the applicant this feature allows the successful induction of a medically useful transdermal immune response (see also page 7, lines 13-16 of the description).
However, the sole example using the compounds as required by claim 1 (b) which has provided in the application as filed is the set of experiments illustrated in Figure 9. As can be read in the legend of said Figure 9, **no protection was observed in these experiments**.
Therefore, the composition defined in independent claim 1 fails to solve the above stated technical problem and hence cannot be considered as being inventive in the sense of Article 33(3) PCT.

2.1 Dependent claims 2-22 which characterise further embodiments of claim 1, claims 23 and 24 which define kits comprising the vaccine composition of claim 1, and claims 25-35 which define different uses of the vaccine composition of claim 1 for the generation of a protective immune response do not appear to introduce subject-matter which would render the subject-matter of said claims inventive in view of the disclosures of D1.
Claims 2-35 thus do not fulfill the requirements of Article 33(3) PCT.

2.2 Claim 36 refers to the use of any **individual** compound as defined in any of the preceding claims for the preparation of a vaccine composition which would induce any immune response. Among **many** other examples, claim 36 combined with claim 11 includes any known and unknown vaccine.
Claim 36 is therefore not novel in the sense of Article 33(2) PCT.

Re Item VIII

Certain observations on the international application

1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved.

1.1 Moreover, claim 1 is not supported by the description as required by Article 6 PCT, as its scope is much broader than justified by the description and drawings, in which only one embodiment which allows the performance of the claimed invention is disclosed, i.e. the use of transfersomes™. Furthermore, some of the conventional lipid vesicles described in the comparative examples also fall within the broad wording of the claim. It is generally accepted that the disclosure of one way of performing an invention is only sufficient if it allows the invention to be performed in the **whole range claimed** rather than only some members of the claimed class to be obtained (see also Item V).

1.2 In addition, as sufficiency of disclosure thus presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims, the present application does not meet the requirements of Article 5 PCT (see also Item V).

2. The extensive use in the claims of the expressions "one or more", "preferably", "and/or", "in particular", "such as", "like", "etc.", "often" and of similar formulations renders the determination of the exact nature of the protection sought nearly impossible. Therefore, claims 1-36 lack clarity in the sense of Article 6 PCT.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* C 2260 PCT

Box No. I TITLE OF INVENTION

Noninvasive vaccination through the skin

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

IDEA AG
Frankfurter Ring 193 a
80807 MUNICH
DE

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CEVC, Gregor
Erich-Kästner-Weg 16
85551 KIRCHHEIM
DE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Vossius & Partner
P.O. Box 86 07 67
81634 MUNICH
DE

(No. 31)

Telephone No. 089-413 040

Facsimile No. 089-413 04 111

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CHOPRA, Amla
A/21A, Ashok Vihar
Ohase 1
Delhi, 110052
IN

This person is:

- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [X] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☐ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☐ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☐ **AE** United Arab Emirates
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☒ **KR** Republic of Korea
☐ **KZ** Kazakhstan
☐ **LC** Saint Lucia
☐ **LK** Sri Lanka
☐ **LR** Liberia
☐ **LS** Lesotho
☐ **LT** Lithuania
☐ **LU** Luxembourg
☐ **LV** Latvia
☐ **MA** Morocco
☐ **MD** Republic of Moldova
☐ **MG** Madagascar
☐ **MK** The former Yugoslav Republic of Macedonia
☐ **MN** Mongolia
☐ **MW** Malawi
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☐ **ZA** South Africa
☐ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....
☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) Jan. 27, 1999 (27.1.99)	99101479.6		EP	
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date (day/month/year)	Number	Country (or regional Office)
19/07/99	99101479.6	EP

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	:52
claims	: 7
abstract	: 1
drawings	:14
sequence listing part of description	: -
Total number of sheets	:78

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Munich, January 26, 2000

Dr. Joachim Wachenfeld
European Patent Attorney

Wa/Mei/mb

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: C 2260 PCT

Applicant: IDEA AG, et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . EUR 102.00 [T]

2. SEARCH FEE . . . . . EUR 945.00 [S]

International search to be carried out by EP

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 78 sheets.

first 30 sheets . . . . . EUR 409.00 [b1]

48 (remaining sheets) x 9.00 (additional amount) = EUR 432.00 [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . EUR 841.00 [B]

Designation Fees

The international application contains 10 designations.

10 (number of designation fees payable *(maximum 10)*) x 88.00 (amount of designation fee) = EUR 880.00 [D]

Add amounts entered at B and D and enter total at I . . . . . EUR 1,721.00 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . EUR 30.00 [P]

5. TOTAL FEES PAYABLE . . . . . EUR 2,798.00 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

[ ] The designation fees are not paid at this time.

MODE OF PAYMENT

[X] authorization to charge deposit account (see below)
[ ] cheque
[ ] postal money order
[ ] bank draft
[ ] cash
[ ] revenue stamps
[ ] coupons
[ ] other *(specify)*:

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ EP

[X] is hereby authorized to charge the total fees indicated above to my deposit account.

[X] *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

[X] is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2800.0321
Deposit Account No.

February 26, 2000
Date *(day/month/year)*

Dr. Joachim Wachenfeld
Signature European Patent Attorney

Wa/Mei/mb

See Notes to the fee calculation sheet